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<p>(21) International Application Number: PCT/IB97/01068</p> <p>(22) International Filing Date: 19 August 1997 (19.08.97)</p> <p>(30) Priority Data: 9618008.8 27 August 1996 (27.08.96) GB</p> <p>(71) Applicant (for all designated States except US): DSM N.V. [NL/NL]; Het Overloon 1, NL-6411 TE Heerlen (NL).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): VAN OUYEN, Johannes, Adrianus, Cornelis [NL/NL]; A.M.A. van Langeraadweg 7, NL-3381 LB Grissenburg (NL).</p> <p>(74) Agent: JACOBS, Monique, Sophie, Nicole; Octrooibureau DSM, P.O. Box 9, NL-6160 MA Geleen (NL).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: BIOCIDAL COMPOSITIONS</p> <p>(57) Abstract</p> <p>This invention relates to a composition comprising benzoic acid or a derivative of benzoic acid capable of giving rise to free benzoic acid <i>in vivo</i> for use as a medicament for animals, wherein said acid/derivative functions as an antibiotic, promotes growth, decreases feed conversion and improves digestibility of amino acids administered in animal feeds. The benzoic acid or its derivative can be administered to the animal either in its feed composition or in its drinking water. It is particularly effective in pigs.</p>		

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BIOCIDAL COMPOSITIONS

This invention relates to the use of compositions comprising benzoic acid for use as a medicament for animals, especially pigs, at the same time promoting growth thereof and improving the digestibility of amino acids fed to such animals.

It is known from our own prior published EP-A-0683985 that animal feed
5 compositions comprising benzoic acid or salts thereof can be used to minimise the emission of odoriferous ammonia from organic wastes, especially animal excrements and manure.

It has now been found that in addition to the above function, benzoic acid can be used instead of relatively expensive antibiotics for such animals and
10 furthermore, such acid/salts have the advantage of being able to promote growth, decrease feed conversion and improve digestibility of amino acids in animal feeds.

Accordingly, the present invention is a composition comprising benzoic acid or a derivative of benzoic acid capable of giving rise to free benzoic acid *in vivo* for use as a medicament for animals.

15 Benzoic acid or a derivative thereof capable of giving rise to benzoic acid *in vivo* may be administered to the animals as a component of a composition which is conventionally fed to animals. Thus, benzoic acid and derivatives thereof may be suitably administered to the animals as a component of the animal feed or in their drinking water. Specific examples of derivatives of benzoic acid which can give
20 rise to benzoic acid *in vivo* include salts of benzoic acid such as eg the alkali metal-alkaline earth metal- and ammonium benzoates.

The amount of benzoic acid or a derivative thereof administered to the animal is suitably such that it is sufficient to prevent/cure any infection in the animal in its capacity as a biocide. Such an amount is suitably in the range from 0.001 -
25 5% based on the total weight of each feed fed to the animal. This amount may,

however, be higher if the function of benzoic acid or a derivative thereof is not only to act as a biocide but also to control the pH of the animal excreta fed on such a diet in order to suppress the emission of ammonia from the excreta. Such higher amounts are suitably limited to a maximum of about 10% based on the total animal feed composition. The benzone acid/salt functions inter alia as an antibiotic, promotes growth, decreases feed conversion and improves digestibility of amino acids administered in animal feeds.

A typical formulation for an animal feed composition is shown in Table 1 below in which all the amounts shown in % by weight were fed to pigs:

TABLE 1

Composition	Control II	Example 2
Meat meal (58% Crude protein)	3.20	3.20
Molasses	5.00	5.00
Wheat	5.90	5.90
Soybean meal (45% Crude protein)	15.1	15.1
Tapioca (66% starch)	36.5	35.5
Wheat middlings	15	15
Animal fat	3.3	3.3
Limestone	0.74	0.74
Lysine hydrochloride (98%)	0.06	0.06
Vitamin premix	0.5	0.5
Trace minerals	0.5	0.5
Sunflower meal	12.2	12.2
Ammonium chloride	2	2
Ammonium benzoate	-	1

Thus, benzoic acid or a derivative thereof may be used in combination with conventional ingredients present in an animal feed composition (diet) such as calcium carbonates, electrolytes such as eg ammonium chloride, proteins such as soya bean meal, wheat, starch, sunflower meal, corn, meat and bone meal, amino acids, animal fat, vitamins and trace minerals.

In such a composition, the ratio of the electrolyte to the benzoic acid or a derivative thereof is suitably in the range from 0.5 : 1 to 5 : 1 w/w, preferably from 1.5 : 1 to 3 : 1 w/w.

Benzoic acid or a derivative thereof is particularly effective as a
 5 medicament for animals such as poultry, pigs or cattle, especially pigs.

The present invention is further illustrated with reference to the following
 Examples:

EXAMPLE 1:

The following feed compositions (shown in Table 2 below) in which all the
 10 amounts shown in % by weight were fed to pigs.

TABLE 2

Composition	Control I	Control II	Example 1
Meat meal (58% Crude protein)	3.20	3.20	3.20
Molasses	5.00	5.00	5.00
Wheat	5.90	5.90	5.90
Soybean meal (45% Crude protein)	15.1	15.1	15.1
Tapioca (66% starch)	38.5	36.5	35.5
Wheat middlings	15	15	15
Animal fat	3.3	3.3	3.3
Limestone	0.74	0.74	0.74
Lysine hydrochloride (98%)	0.06	0.06	0.06
Vitamin premix	0.5	0.5	0.5
Trace minerals	0.5	0.5	0.5
Sunflower meal	12.2	12.2	12.2
Ammonium chloride	-	2	2
Ammonium benzoate	-	-	1

The pH of the urine of the pigs fed on these diets for two days was
 15 monitored over various durations and found to be as follows (see Table 3 below):

TABLE 3

Duration	Control I - pH	Control II - pH	Example 2 - pH
After 0 Days*	8.15	5.22	4.68
After 7 days	8.30	8.57	5.01
After 10 days	8.30	8.60	6.92

*First excretion by the pigs after the two day feeding stage.

From these results it is abundantly clear that the use of the additives of the present invention gives rise to excrements of highly acidic and stable pH values and consequently gives rise to little or no ammonia emissions.

EXAMPLE 2:

In a further comparative test, a number of pigs were fed with a standard feed as shown below in Table 4. This was repeated in Example 2 except that 0.7% wt. of the wheat middlings in the standard feed was replaced with benzoic acid. The results are shown in Table 5 below:

TABLE 4

Composition	Weight %
Barley	36.15
Wheat	30
Peas	3.5
Rape seed oil meal	3
Soyabean oil meal (Brazilian)	17
Wheat middlings	2.5*
Animal fat	1.9
Limestone	0.61
Lysine hydrochloride (98%)	0.18
Vitamin premix	1
Molasses	3.4
Methionine	0.11
Mono-calcium phosphate	0.4
Salt	0.25

TABLE 5

Variables	Example 2*	Comparative Test
No. of pigs fed	33	33
Starting wt. per pig (Kg)	23.8	23.0
Final wt. per pig (Kg)	40	40.3
Growth per pig per day (g)	577	588
Feed conversion	1.91	2.11
Feed intake (Kg)	1.104	1.239

*0.7% wt of the wheat middlings in the standard feed replaced by benzoic acid.

- The above results show that pigs fed with a diet comprising benzoic acid have a much lower feed conversion (calculated as a ratio of feed intake over growth per pig per day) than those fed on a diet free of such benzoic acid. This signifies that the feed to the pigs is being used more efficiently.

Example 3:

- The effect of the experimental feed containing benzoic acid on the performance of the pigs was compared with the control feed which did not contain any benzoic acid. A pig room with six pens was used for this example during three periods. In three pens pigs were fed with the control feed, and in the other three pens pigs were fed with the experimental feed. The feed compositions are shown in the Table 6 and the performance results are shown in Table 7 below. It can be seen from Table 7 that the pigs fed on the experimental feed had a significant lower feed conversion ratio. This is probably due to the lower pH in the intestine which perhaps improves digestibility.

TABLE 6**Raw materials (%) and the calculated chemical composition of the feed (g/kg)**

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Components	Starting Feed		Finishing Feed	
	Experimental	Control	Experimental	Control
Rye	5.0	5.0	15.0	15.0
Barley	30.0	30.0	15.0	15.0
Wheat	27.8	27.2	25.0	24.2
Peas	3.5	3.5	14.5	13.0
Maize gluten feed	-	-	7.1	6.5
Rape seed middlings	3.0	3.0	2.3	2.5
Soya meal	15.2	14.0	6.5	7.3
Wheat middlings	2.8	4.4	5.0	5.0
Cane sugar molasses	5.0	5.0	3.2	6.0
Animal meal	1.3	2.0	-	-
Animal fat	1.90	1.83	2.20	2.21
Mixture of methionine and cystine (Mervit®)	0.55	0.56	0.35	0.36
Threonine (Mervit®)	0.26	0.29	0.29	0.30
Liquid Lysine	0.76	0.78	0.56	0.57
Calprona P®*	1.0	0.70	0.6	-
Monocalcium phosphate	0.33	0.22	-	0.02
Sodium chloride	0.22	0.21	0.25	0.24
Vitamin/Mineral pre-mix (Mervit®) for starting feed	0.50	0.50	-	-
Vitamin/Mineral pre-mix (Mervit®) for finishing feed	-	-	0.50	0.50
Phytase enzyme (Mervit®)	0.20	0.24	0.21	0.20
Limestone	-	0.55	-	1.13
Benzoic acid	0.7	-	1.4	-

*-It is a blend of Ca (25%) and a mixture of carboxylic acids (75%) - the acids and their amounts in the mixture being formic (30%), acetic (30%) propionic (30%) and citric (10%).

Calculated Chemical Composition

Components	Starting Feed		Finishing Feed	
	Experimental	Control	Experimental	Control
Energy Value#	1.08	1.08	1.07	1.07
Water	131	132	130	134
Digestible lysine	8.4	8.4	7.0	7.0
Digestible methionine and cystine	5.2	5.2	4.5	4.5
Starch	380	380	400	388
Calcium	7.3	7.3	6.3	6.3
Phosphorus	4.8	4.8	4.1	4.1
Digestible phosphorus	2.9	2.9	2.1	2.1
Sodium	1.2	1.2	1.3	1.4
Potassium	9.0	9.0	8.3	9.1
Chlorine	3.2	3.2	3.0	3.4
Contents per kg				
Crude Protein	169	170	150	150
Crude fat	39	40	41	41
Crude fibre	39	40	40	39
Ash	50	53	44	53

5 # - Unit Energy value = 8.8 MJ net available energy for pigs for production and maintenance

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TABLE 7**Performance of Experimental Pigs**

	Control Feed	Experimental Feed
Number of pigs	99	99
Initial live weight (kg)	26.2	26.29
Final live weight (kg)	107.4	108.2
Growth rate (g/day)	723	738
Feed intake (kg/day)	1.97	1.95
Feed conversion rate	2.72	2.64
Meat percentage	56.1	56.3
Culled pigs	5	2

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Claims:

1. A composition comprising benzoic acid or a derivative of benzoic acid capable of giving rise to free benzoic acid *in vivo* for use as a medicament for animals.
2. A composition according to Claim 1 wherein benzoic acid or a derivative thereof capable of giving rise to benzoic acid *in vivo* is administered to the animals as a component of an animal feed composition.
3. A composition according to Claim 1 wherein benzoic acid and derivatives thereof are administered to the animals as a component of the drinking water fed to the animals.
4. A composition according to any one of the preceding Claims wherein derivatives of benzoic acid which can give rise to benzoic acid *in vivo* are salts of benzoic acid selected from the alkali metal benzoates, alkaline earth metal benzoates and ammonium benzoate.
5. A composition according to any one of the preceding Claims wherein the amount of benzoic acid or a derivative thereof administered to the animal is such that it is sufficient to act as a biocide.
6. A composition according to any one of the preceding Claims wherein the amount of benzoic acid or a derivative thereof is limited to a maximum of about 10% based on the total animal feed composition.
7. A composition according to any one of the preceding Claims wherein the amount of benzoic acid or a derivative thereof administered to the animal is in the range from 0.001 - 5% based on the total weight of each feed fed to the animal.
8. A composition according to any one of the preceding Claims wherein the benzoic acid or a derivative thereof is administered to the animal in combination with one or more of the following ingredients present in an animal feed

composition (diet): calcium carbonates; electrolytes including *inter alia* ammonium chloride; proteins including *inter alia* soya bean meal, wheat, starch, sunflower meal, corn, meat and bone meal; amino acids; animal fat; vitamins; and trace minerals.

- 5 9. A composition according to Claim 8 wherein the ratio of the electrolyte to the benzoic acid or a derivative thereof in the animal feed composition is in the range from 0.5 : 1 to 5 : 1 w/w.

10. A formulation for an animal feed composition as shown in the Table below in which all the amounts shown in % by weight:

10

Composition	Amounts
Meat meal (58% Crude protein)	3.20
Molasses	5.00
Wheat	5.90
Soybean meal (45% Crude protein)	15.1
Tapioca (66% starch)	35.5
Wheat middlings	15
Animal fat	3.3
Limestone	0.74
Lysine hydrochloride (98%)	0.06
Vitamin premix	0.5
Trace minerals	0.5
Sunflower meal	12.2
Ammonium chloride	2
Ammonium benzoate	1

11. A an animal feed composition comprising benzoic acid or a derivative thereof whenever administered as a medicament for animals selected from poultry, pigs and cattle.

- 15 12. A composition according to any one of the preceding Claims wherein benzoic acid is used in a pig feed formulation comprising the components shown in Tables 4 and 8 below:

20

TABLE 4

Composition	Weight %
Barley	36.15
Wheat	30
Peas	3.5
Rape seed oil meal	3
Soyabean oil meal (Brazilian)	17
Wheat middlings	2.5*
Animal fat	1.9
Limestone	0.61
Lysine hydrochloride (98%)	0.18
Vitamin premix	1
Molasses	3.4
Methionine	0.11
Mono-calcium phosphate	0.4
Salt	0.25

TABLE 8

Variables	Amounts*
No. of pigs fed	33
Starting wt. per pig (Kg)	23.8
Final wt. per pig (Kg)	40
Growth per pig per day (g)	577
Feed conversion	1.91
Feed intake (Kg)	1.104

*0.7% wt of the wheat middlings in the standard fee replaced by benzoic acid.

INTERNATIONAL SEARCH REPORT

Int. l. Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/19 A23K1/16 A23K1/18

According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K A23K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☒ Further documents are listed in the continuation of box C.

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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